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We developed artificial neural network (ANN) techniques to predict breast lesion malignancy and invasion based on mammographic features extracted by radiologists and by computerized image processing techniques. We incorporated the radiologist impression as an input to the malignancy-predicting ANN, which outperformed the radiologists (A_z of 0.89 vs. 0.85, p=0.07). We developed a semi-automated technique for extracting and characterizing breast mass margins, and incorporated those features into an ANN to predict malignancy. In preparation for developing ANNs for feature extraction, we explored the underlying behavior of the previous ANNs by examining their error surfaces in weight space. Finally we developed a novel ANN which predicts invasion among malignant breast lesions based on BI-RADS mammographic findings and patient age. This ANN performed well with A_z of 0.91 ± 0.03. Together these four studies provided important new information which will be crucial toward developing a complete system for computer-aided diagnosis of breast cancer.

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Table of Contents

1. Introduction

1.1. Significance of diagnostic problem

In the U.S. in 1994, there were approximately 182,000 new cases and 46,000 deaths due to breast cancer, making it second only to lung cancer as the cause of cancer death among women [1]. Mammography is the modality of choice for early detection of breast cancer and can significantly decrease the mortality for women undergoing screening [2,3]. Evaluating mammograms remains a challenging task to radiologists, however, as they consider many radiographic and non-radiographic features in order to decide whether a lesion is benign or whether it should be followed or biopsied. Although mammography is very sensitive, there are a large number of false-positive biopsies. Of women with radiographically-suspicious, nonpalpable lesions who are sent to biopsy, only 15 to 34% actually have a malignancy by histologic diagnosis [4,5].

1.2. Potential of the proposed technique

This study seeks to improve the diagnosis and treatment of breast cancer by reducing the cost and morbidity of unnecessary biopsies. Cost is a major obstacle to widespread acceptance of mammographic screening [6]. It has been shown that surgeon's fees and biopsy costs account for over half the cost of detecting small breast cancers in a screening population [7]. Preventing unnecessary biopsies is therefore one of the most important ways to improve the efficacy of mammographic screening. Many previous reports have discussed the need to reduce the number of benign biopsies [8,9].

To improve early diagnosis, we propose an automated computer-aided diagnosis (CADx) system for mammography. The system will perform automated feature extraction from mammograms using artificial neural network (ANN) and other image processing techniques, then predict the outcome of biopsy (benign vs. malignant). The intent is to identify probably benign lesions for which biopsies may be spared. This study will potentially provide an accurate, consistent aide for the early diagnosis of breast cancer.

1.3. Computer-aided diagnosis using artificial neural networks

In medical imaging, CADx systems provide radiologists with information from computerized analysis of images or image features, thus helping radiologists detect or diagnose diseases more accurately, easily, and consistently [10,11]. In mammography, there have been numerous reports on computerized detection [12-18] or diagnosis [19-24] of breast cancer. Although both are generally considered CADx systems, detection systems locate suspicious lesions in an image, while diagnosis systems such as this study determine whether those lesions are benign or malignant.

This study focuses on the use of artificial neural networks (ANNs) which are computer models inspired by the structure and function of biological neural networks,

such as the cerebral cortex of the human brain. Most ANNs are characterized by multiple, simple computing elements or *neurons* that work in parallel. The neurons interact globally through connections that have strengths or *weights*, and together they can duplicate aspects of human intelligence while incorporating the processing power of computers [25]. The classification rules are not defined *a priori*. instead the network is trained by presenting it with medical findings and final diagnoses from many patients. The network "learns" by adapting its weights to improve its diagnosis for each patient, just as physicians become more experienced with time. Once trained, the network can generalize to new patients it has not seen before.

ANNs are very useful in handling complex decision tasks such as those involved in medical diagnoses, where multiple findings are subtly related in ways which are often difficult to express in the form of diagnostic criteria. The networks can capture such relationships between the input findings to generate robust outputs. ANNs solve problems empirically without requiring any prior knowledge of distribution functions or any type of statistical modeling, yet ANNs are able to duplicate solutions of statistical methods [26]. Finally, ANNs are always consistent, for they are not prone to human fatigue or bias.

1.4. Summary of progress from previous budget period.

During the first budget period, our institute adopted the Breast Imaging Reporting and Data System or BI-RADS lexicon, which was endorsed by the American College of Radiology to improve upon the consistency of mammographic reports [27,28]. The use of BI-RADS descriptors would allow the techniques developed in this study to be used in all institutions that adopt this standardized system. We investigated the use of this new lexicon to take advantage of its potential for general applicability of the CADx system. This work was presented at a national conference [29] and subsequently published in two parts in a peer-reviewed journal [30,31]. The ANN was developed using 206 patients who underwent excisional biopsy and pathologic diagnosis. The ANN was evaluated by receiver operating characteristic (ROC) analysis and its performance was compared to that of expert mammographers. That study was then extended by identifying an optimal subset of input features to simplify the network. This work was presented at two national conferences [32,33] and subsequently published in a peer-reviewed journal [34].

1.5. Technical Objectives

The technical objectives pertaining to the *second* budget period are aims 2a and 2b from the list of aims for the entire budget period shown below:

(1) ***Identify an optimal subset of features that would provide adequate diagnostic performance.***
  - 1a. Retrain the features-to-diagnosis ANN using sub-groups of features. The goal is to maintain the sensitivity of the original network while keeping specificity reasonably high.
  - 1b. Encode the multiple-value features into binary "sub-features", then repeat step 1a to reduce the number of sub-features. The sub-features will be easier to extract by automated schemes.

(2) ***Investigate conventional and ANN methods for extracting the optimal subset of features directly from mammograms.***
  - 2a. Implement established techniques which have demonstrated promise for extracting features belonging to our reduced feature set.
  - 2b. Investigate several ANN techniques for feature extraction, focusing on features which may be difficult to classify by conventional techniques in step 2a. For both 2a and 2b, evaluate these techniques by comparing the extracted features against radiologists' findings.

(3) ***Evaluate the automated CAD system clinically.***
  - 3a. Implement the CAD system by feeding the best feature extraction techniques from step 2 into the best features-to-diagnosis ANN from step 1, and compare the resulting diagnosis against the biopsy result.
  - 3b. Evaluate the accuracy of the CAD system retrospectively by using patient records from our computerized mammography database.

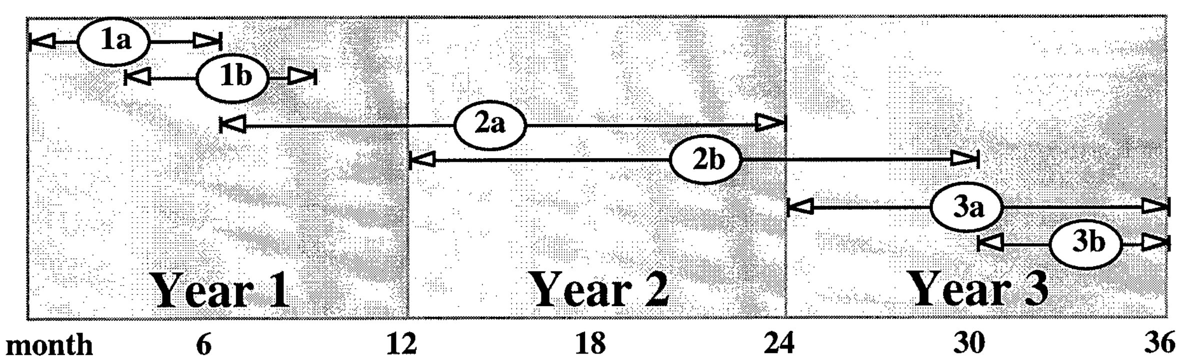


Figure 1. Time line for proposal project period.

In the following sections, we will report in detail on the progress in aim 2a and 2b.

2. Body

The original hypothesis of this proposal was to identify a small number of important radiologist-extracted mammographic findings, then attempt to extract those findings using artificial neural network (ANN) or classic image processing techniques. Our work during the current, second budget period has revealed two major new discoveries which affect that hypothesis. First, we discovered significant new potential in utilizing radiologist-extracted findings to predict malignancy as well invasion among breast lesions. Second, our initial attempts at feature extraction did not yield the level of performance required for an accurate, automated computer-aided diagnosis system. For these reasons, we have increased the emphasis on using radiologist-extracted findings to provide the best possible diagnosis of breast cancer.

In the following sections, we will describe four major studies undertaken during the second budget period:

2.1) We used the radiologist's impression as an input feature to the ANN. This work was presented at the Radiological Society of North America (RSNA) '95 annual meeting and published in the proceedings issue of *Radiology* [35].

2.2) We used global thresholding to extract the mass margin feature, and also presented this work at RSNA '95 for publication in the proceedings [36].

2.3) We studied the error surfaces of ANNs using the optimized subset of findings identified in the first budget period. This work was presented at the World Congress of Neural Networks (WCNN) '96 conference [37].

2.4) We explored the feasibility of extending the original ANN which used radiologist-extracted findings to predict breast lesion malignancy so that it would also predict whether malignant lesions are invasive or in situ carcinoma. This work was presented at the International Society for Optical Engineering SPIE Medical Imaging 1996 conference [38] and was accepted for publication in *Radiology* [39].

The first two studies were undertaken to address specific aim 2a, while the second two studies address specific aim 2b, with our new emphasis on radiologist-extracted findings.

2.1. ANN incorporating radiologist impression as an input.

The purpose of this study was to develop an ANN as a diagnostic aide in mammography, predicting breast lesion malignancy based on the radiologist impression and an optimized subset of BI-RADS™ radiographic features. Until now all CADx studies follow one of two paradigms, either pitting ANN output vs. radiologist diagnosis, or encouraging the radiologist to incorporate the ANN output into her final diagnosis. This study explores a novel option in which the ANN considers the radiologist diagnosis as an input finding along with the optimized subset of BI-RADS

findings previously identified. The use of the radiologist impression as an input was justified since the network was intended to assist the radiologist in making a diagnosis. Since the radiologist impression is based on the human expert's consideration of the mammograms, clinical findings, and general experience, we hypothesized that it may provide important diagnostic information for the ANN.

A 3-layer backpropagation ANN was developed to predict the outcome of biopsy using only 4 features: 3 from the BI-RADS lexicon (mass margin, calcification description, and age) plus the radiologist impression. This ANN architecture and the network training algorithm have been described in detail in the proposal. The choice of those three particular BI-RADS findings was arrived at after an optimized reduction of the number of input features, as described in the previous year's progress report. Using the round robin or leave-one-out technique with 206 patients, network performance was evaluated by A_Z, the receiver operating characteristic (ROC) area index.

We found that given age and the 2 radiographic features but not the radiologist impression, the ANN performed with A_Z=0.83, which was not significantly worse than the expert mammographer's A_Z=0.85. Given the additional input of the radiologist impression, the network's A_Z=0.89 was significantly better than the radiologists' performance, with p=0.07. In figure. 2, the ROC curves for the 4-feature ANN given the radiologist impression and the radiologist impression itself are compared.

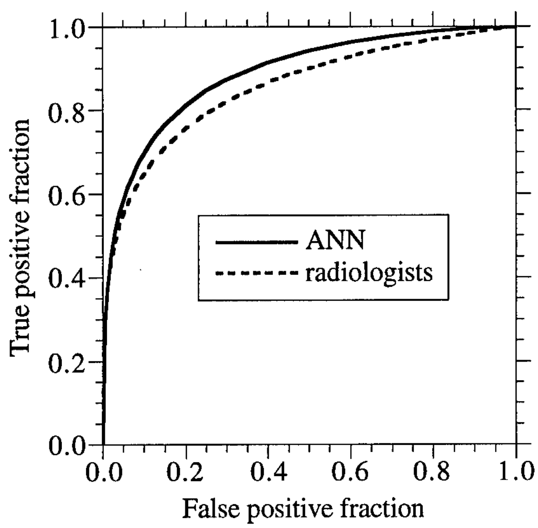


Fig. 2. ROC curves of 4-feature ANN incorporating the radiologist impression versus the radiologist impression itself. The ANN out-performed radiologists with p=0.07.

In conclusion, a diagnostic aide was developed for mammography that accurately predicted malignancy given only 4 input features, including the radiologist impression. By taking advantage of the radiologists' considerable expertise, the combined system was more accurate than radiologists alone.

2.2. Extraction of mass margin by global thresholding

In the first budget period of this proposal, we have already demonstrated ANNs which predict breast mass malignancy based on only patient age and the mass margin finding extracted by radiologists. The purpose of this study was to attempt to replace this very important mass margin finding with one or two computer-extracted features.

For this study, 41 mammograms with biopsy-proven masses were randomly selected. The mammograms were digitized to 100 micron per pixel resolution, and a 512 by 512 pixel region of interest (ROI) centered at the mass was extracted. To facilitate the extraction of the boundary of each mass, the background trend in the ROI was fitted to a second-order polynomial and subtracted, and the ROI was further median filtered to reduce noise. Starting from the center of the mass, possible mass boundaries were identified using a combination of region growing and global thresholding techniques. The results from each iteration are displayed to the user as a false color image. The user determines which color-coded threshold most closely approximates the boundaries of the mass. In other words, the final mass boundary is manually selected from many automatically generated candidates.

Given the mass boundary, the irregularity and circularity are calculated in a straightforward manner. The irregularity is defined as the ratio of the perimeter of the mass to that of a circle of equal area. The circularity is defined as the fraction of overlap in area between the mass and a centered circle of equal area. The hypothesis is that well-circumscribed and thus probably benign masses will be characterized by low irregularity and high circularity, while the opposite trends will apply to spiculated masses.

We found the ANN performed reasonably well with A_Z of 0.82 ± 0.07 when given the two findings of patient age and irregularity. This performance was somewhat improved to A_Z of 0.89 ± 0.06 when the ANN was given circularity as an additional, third input feature. Both of these ANNs were much worse, however, when compared to an ANN based on age and the radiologist-extracted mass margin, which performed with A_Z of 0.96 ± 0.03. It should be noted that for this limited sample of masses, the expert radiologists' impressions distinguished benign from malignant masses perfectly with A_Z of 1.0.

These results were not very successful for several reasons. Unlike our previous studies, these ANNs did not match or outperform the radiologists that they are intended to assist. Since our expert radiologists already diagnose masses with very high accuracy, there is in fact very little room for improvement. Finally, there was relatively low correlation between the findings extracted by radiologists vs. computer. We have initiated attempts to improve these results by using more sophisticated measures of texture and shape such as fractal dimension analysis. We have also increased the number of digitized mammograms from 41 to 100 to reduce the large standard of deviation associated with the ROC areas.

2.3. Error surfaces of simplified ANN.

The purpose of this study was to investigate the underlying behavior of an artificial neural network (ANN) for computer-aided diagnosis in mammography. A single-layer perceptron was developed to predict whether masses were benign or malignant, based only on the patient age and the mass margin finding characterized by radiologists. The performance of this very simple ANN was comparable to much more complex ANNs which required many more features. The network's three-dimensional error surfaces were visualized by independently varying the perceptron's two weights and bias value, while measuring performance by mean squared error and ROC area index. This study provided a unique opportunity to study the underlying behavior of an actual ANN medical application, which will assist in development of other ANNs for computer-aided diagnosis in mammography.

From 266 randomly selected patients who underwent biopsy, 138 cases had masses. Expert radiologists characterized the mass margin as 1 of 5 categories (in increasing order of suspicion: well circumscribed, microlobulated, obscured, indistinct, or spiculated) and the patient age was recorded. The round robin or "leave one out" data sampling technique was used as before. The network employed was a single-layer perceptron with only 2 inputs, the mass margin and patient age, and a bias term.

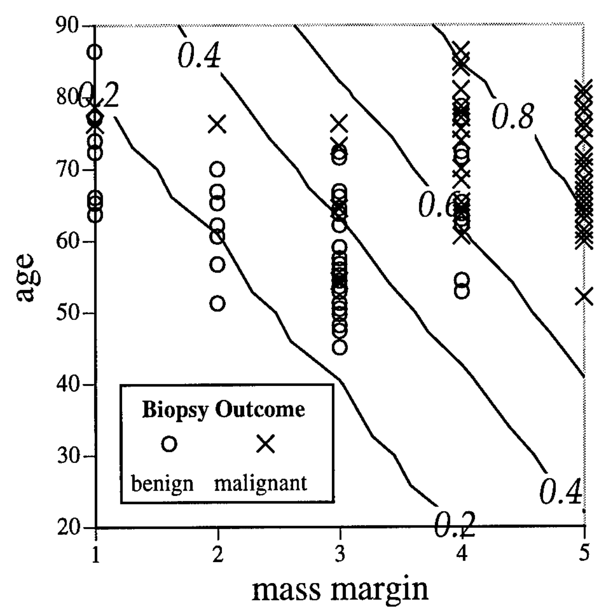


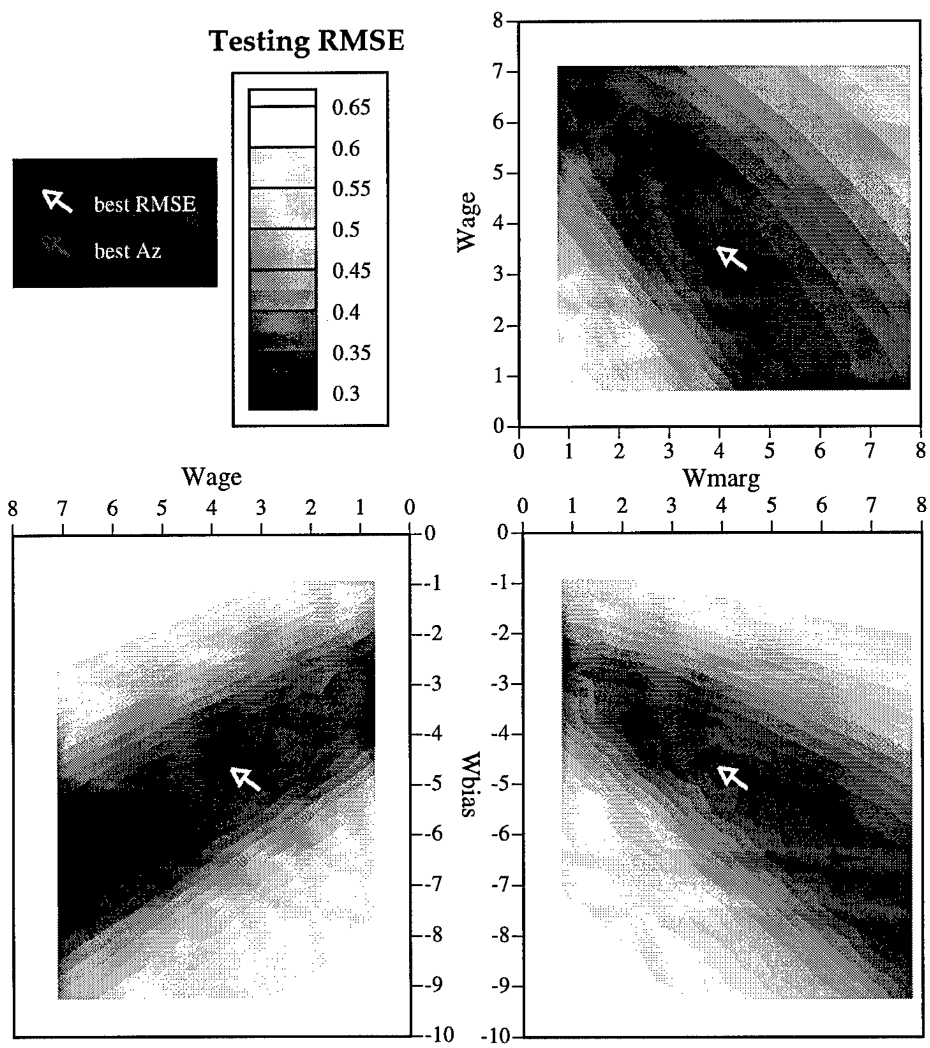
Fig 3. Feature space: input patterns vs. network outputs

The input patterns are superimposed over a contour plot of the trained network's outputs over the entire range of the 2 inputs, mass margin and patient age. The patterns belong to 1 of 2 classes, benign or malignant, shown as circles and x marks respectively. Malignancies tend to occur for older patients with high mass margin values (upper right portion of graph). The 2-input perceptron with sigmoidal thresholding generated continuous, linear hyperplanes depicted as contours. Since the 2 pattern classes overlap, it is not possible to separate them by any hyperplane , so any chosen threshold

is necessarily a trade-off between sensitivity and specificity. Lower thresholds of the network outputs would yield higher sensitivity (detecting more cancers), while higher thresholds would produce higher specificity (fewer false positive biopsies). Usually low thresholds are chosen to ensure cancer detection.

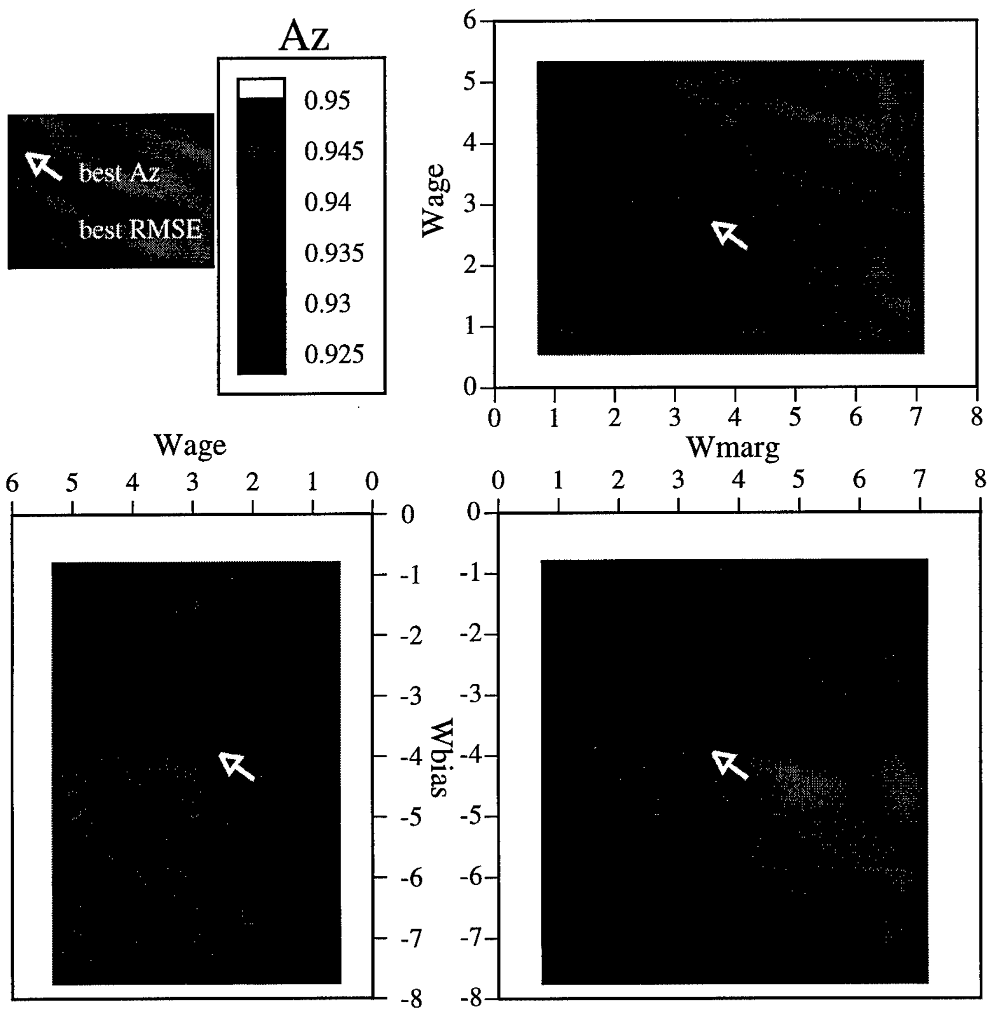
Figs. 4a/4b visualize the network's error surfaces in 3-dimensional weight space (1 weight each for the mass margin, age, and bias). Performance was evaluated by doing a grid search over a range of weights and plotting the testing RMSE and Az against all 3 combinations of 2 weights at a time. The best weights are indicated with white arrows in each plot, and for comparison the best weights from the opposite plots are shown in gray. Note the striking differences in both the coordinates for the best weights as well as the underlying error surfaces. This distinction is important because most computer-aided diagnosis applications are evaluated in terms of Az rather than MSE.

Fig 4a. Error surfaces in weight space (testing RMSE)



Since the perceptron minimized training MSE, not surprisingly the testing RMSE surfaces were also well behaved with no local minima and an obvious global minimum (shown as trenches of deep gray). In comparison, the Az plots revealed a large, irregularly shaped global maximum. Because the perceptron convergence algorithm optimized MSE rather than Az, the white arrows indicating the weights for the best Az were actually quite far from the actual global maximum. Fortunately, Az performance was very good over a wide range of weights, so the suboptimal network solution still performed nearly as well as actual global maximum. This study demonstrated that it is important to be aware that optimizing ANNs by MSE may not necessarily result in optimization of the A_z.

Fig 4b. Error surfaces in weight space (Az)



2.4. Predicting invasion of breast cancers.

The purpose of this study was to develop an ANN to predict breast cancer invasion based on BI-RADS mammographic findings and age. For patients classified as having invasive breast cancer, excisional biopsy may be obviated by obtaining histologic confirmation via stereotaxic needle core biopsy, and the patients may then undergo a single-stage surgery for mastectomy and/or axillary dissection.

The three studies described above focus on obviating benign biopsies. Additionally, as many as 80% of biopsied malignancies are invasive [40]. Traditionally, these patients require a diagnostic excisional biopsy/lumpectomy, followed by the second, therapeutic surgical procedure of mastectomy and/or axillary dissection. For these invasive cancers, stereotaxic biopsy has also been proposed to provide histologic diagnosis in lieu of excisional biopsy, so that the patients may undergo a single-stage therapeutic surgical procedure for the mastectomy and/or axillary dissection [41,42]. Compared to excisional and stereotaxic biopsy, the current study proposes an artificial neural network (ANN) computer model to provide similarly accurate diagnosis while being completely noninvasive and involving no surgical procedures. This ANN can assist radiologists and surgeons in predicting invasion among nonpalpable, mammographically suspect lesions.

As before, 266 biopsied lesions were randomly selected (96 malignant, 170 benign). Based on 9 BI-RADS mammographic findings and patient age, a 3-layer backpropagation network was developed to predict whether the 96 malignant lesions were in situ or invasive. Performance was measured by A_Z using the round robin sampling technique as before.

Using the 96 biopsy-proven malignant cases, the network distinguished between invasive and in situ cancers very well with A_Z of 0.91 ± 0.03. The ROC curve for this network is shown in Fig. 5, and the histogram of neural network outputs for all cases is shown in Fig. 6, both on the following page.

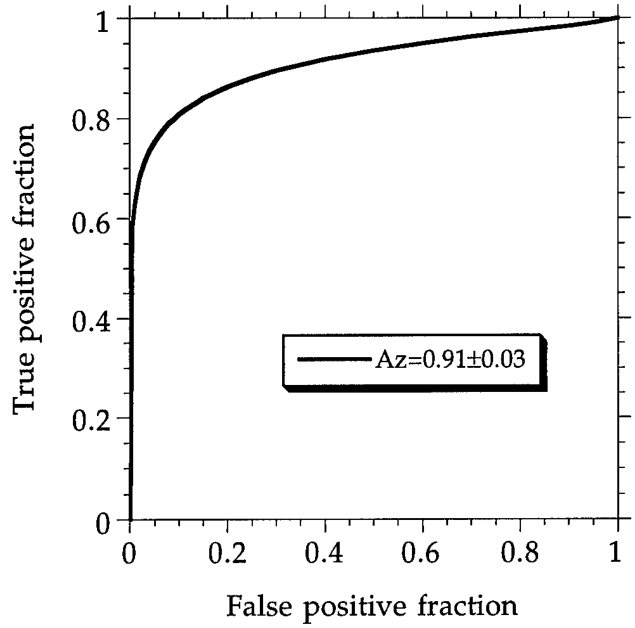


Figure 5. ROC curve for ANN predicting invasion.
The area under the curve, A_z, of 0.91 indicated that the network predicted invasion with a very high degree of accuracy.

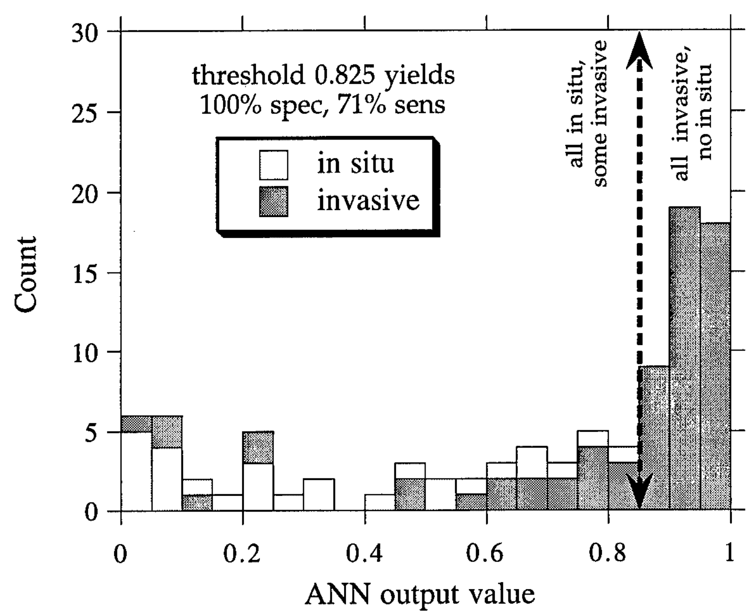


Figure 6. Histogram of ANN outputs for malignant cases only

Note the threshold denoted by the dashed line. Outputs for all in situ cancers were below that threshold and thus correctly classified (100% specificity), while 48 of 68 invasive cancers were above the threshold and thus also correctly classified (71% sensitivity).

The current study demonstrated that BI-RADS mammographic features and patient age could be used to develop an artificial neural network that distinguishes between in situ versus invasive carcinoma. For patients similar to those considered in this study, the network would correctly identify 100% of in situ cancers and 71% of invasive cancers.

Compared to previous studies, this work is unique and important in several respects. By using the BI-RADS lexicon to encode morphological features, the neural networks developed in this study should be applicable to other institutions which have adopted this standard. Moreover, this study was the first to develop a multivariate predictive model using readily available medical findings, i.e., BI-RADS mammographic features and patient age, to accurately classify invasion among breast cancers. By providing information which was previously available only through biopsy, the artificial neural network may assist in surgical planning for patients with breast lesions, and may reduce the cost and morbidity of "unnecessary" surgical biopsies.

3. Conclusions

This goal of this proposal is to develop a computer-aided diagnosis system to automatically extract radiographic features from the mammogram, then use an artificial neural network (ANN) to merge those features to predict breast lesion malignancy. During the first budget period, we successfully developed an ANN that merges radiologist-extracted features to predict malignancy. We also identified an optimal subset of input features while maintaining diagnostic accuracy.

During the current, second budget period, we accomplished four studies. In accordance with specific aim 2a, we improved the performance of the ANN using the optimized subset of findings by incorporating radiologist impression as an additional input finding, as summarized in section 2.1. above. In section 2.2, we described a semi-automated technique using classic image processing techniques to extract and characterize the boundary of breast masses, and developed ANNs using those boundary findings. In accordance with specific aim 2b, we explored the use of ANN techniques for computer-aided diagnosis of breast cancer. In section 2.3, we studied the underlying behavior of these networks by examining their error surfaces in weight space. As discussed in the preamble to section 2, due to the less promising results of the automated feature extraction approach coupled with the highly promising results from using radiologist-extracted BI-RADS findings, we increased our emphasis on the latter approach. Specifically in section 2.4, we developed an ANN to predict invasion among breast malignancies. Together, these studies provide important new discoveries which are crucial for a complete system for the computer-aided diagnosis of breast cancer.

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